

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 16 November 2000 (16.11.00)	
International application No. PCT/EP99/02268	Applicant's or agent's file reference MM/99030/PCT
International filing date (day/month/year) 29 March 1999 (29.03.99)	Priority date (day/month/year)
Applicant MARINO, Maria et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 04 October 2000 (04.10.00)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Juan Cruz Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MARCHI & PARTNERS S.R.L.
Via Pirelli, 19
20124 Milano
ITALIE

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NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year) 29.03.2001

Applicant's or agent's file reference
MM/99030/PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP99/02268

International filing date (day/month/year)
29/03/1999

Priority date (day/month/year)
29/03/1999

Applicant
TECNOGEN S.C.P.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

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Authorized officer

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MM/99030/PCT	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP99/02268	International filing date (day/month/year) 29/03/1999	Priority date (day/month/year) 29/03/1999
International Patent Classification (IPC) or national classification and IPC C07K14/47		
Applicant TECNOGEN S.C.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 04/10/2000	Date of completion of this report 29.03.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80296 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Roscoe, R Telephone No. +49 89 2399 2554



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/02268

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).):*

Description, pages:

1-12 as originally filed

Claims, No.:

1-3 as originally filed

Sequence listing part of the description, pages:

1-3, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP99/02268

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-3
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-3
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-2
	No:	Claims	3

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/02268

V. Reasoned statement on Novelty, Inventive Step and Industrial Applicability

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

- Novelty (Art.33(2) PCT)

Since the present claims are limited to specific peptides which are not disclosed in the prior art, and to uses thereof, novelty is acknowledged.

- Inventive Step (Art.33(3) PCT)

D1 teaches that MBP p87-99 reactive T cell clone - mediated EAE could be ameliorated using a peptide wherein position 96 had been converted P>A. It is noted that changes at positions corresponding to positions 88-90 of applicants Seq. ID No.15 resulted in a peptide unable of alleviating disease condition. Hence, not obvious that peptides of invention would work as all 4 peptides claimed have at least 1 change in these positions.

D2 teaches truncation of the immunodominant epitope of MBP to a size too small to stimulate an antigenic response (approx. 9 aa), yet sufficient to anergize autoreactive T cells. No suggestion to modify longer peptides as in application.

D3 teaches the basic technology of placing glycine residues at every second position in an antigenic peptide, and also the fact that reverse peptides are equally useful. Applicant has applied this technology to the field of MS treatment by tolerization. However, neither D3, nor the cited documents dealing with MS treatment suggest applying this technology for tolerizing peptides in MS.

In view of the cited prior art, inventive step is acknowledged.

- Industrial Applicability (Art.33(4) PCT)

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/02268

For the assessment of the present claims 3 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 3 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

- Certain observations (Support in the Description, Art.6, PCT)

Peptide of Seq.ID No.1 is clearly effective (see p.12) in treatment of experimental MS model. This does not apply to peptide Seq.ID No.2, since this peptide results in a slight delay in onset but a significantly higher severity than when p81-100 known underlying peptide sequence is used (i.e. Seq.ID No.2 does not provide an improved peptide over the closest prior art). Based on the teaching of D3 it is credible that a reverse equivalent of Seq.ID No.1 could function as Seq.ID No.1, yet Seq.ID No.3 is unlikely to be better than Seq.ID No.2. Hence, insofar as claims relate to Seq.ID Nos 2 and 3, it is considered that there is no support for their use as improved peptides for treating MS. Seq.ID No.4 is presumably meant to be the reverse of Seq.ID No.1, however due to a double Gly this is not entirely the case and there is thus no guarantee of functionality. Hence, also in this case there is a lack of support.

This objection could also be raised as an inventive step objection, since it can be argued that these peptides do not solve the problem underlying the present invention. It is noted that in D3, where it is taught that both peptides having all odd or all even positions replaced with glycine are equally effective, an experimental peptide is injected and simple antibody response thereto i.e. to both sides of the peptide chain, taking a planar view, is studied. In MS, the disease is linked to interactions with a folded protein with a particular epitope. Hence the

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/02268

epitope located on the "opposite side" of the peptide chain may not be relevant in this case.

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference MM/99030/PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/EP 99/ 02268	International filing date (day/month/year) 29/03/1999	(Earliest) Priority Date (day/month/year)
Applicant TECNOGEN S.C.P.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☒ contained in the international application in written form.

☒ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

PEPTIDES USEFUL IN TREATING MULTIPLE SCLEROSIS AND A PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☐ None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 99/02268

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 3 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

P/SEP 99/02268

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07K14/47 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>BROCKE S ET AL: "TREATMENT OF EXPERIMENTAL ENCEPHALOMYELITIS WITH A PEPTIDE ANALOGUE OF MYELIN BASIC PROTEIN" NATURE, GB, MACMILLAN JOURNALS LTD. LONDON, vol. 379, no. 6563, page 343-346 XP000601452 ISSN: 0028-0836 cited in the application the whole document</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1-3

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier document but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
 "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
 "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
 "&" document member of the same patent family

Date of the actual completion of the international search

22 November 1999

Date of mailing of the international search report

03/12/1999

Name and mailing address of the ISA

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Authorized officer

Groenendijk, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/02268

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	KARIN E.A.: "Short peptide-based tolerogens without self-antigenic or pathogenic activity reverse autoimmune disease " JOURNAL OF IMMUNOLOGY, vol. 160, no. 10, 15 October 1998 (1998-10-15), pages 5188-5194, XP002123434 BALTIMORE US the whole document -----	1-3
A	EP 0 779 297 A (TECNOGEN SCPA) 18 June 1997 (1997-06-18) the whole document -----	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

EP 99/02268

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0779297 A	18-06-1997	IT MI952582 A US 5932692 A	11-06-1997 03-08-1999